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Associations between mood instability and emotional processing in a large cohort of bipolar patients

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Running title: Mood instability and emotional bias in BD

ABSTRACT

Background: Aberrant emotional biases have been reported in bipolar disorder (BD), but results are inconsistent. Despite the clinical relevance of chronic mood variability in BD, there is no previous research investigating how the extent of symptom fluctuations in bipolar disorder might relate to emotional biases. This exploratory study investigated, in a large cohort of bipolar patients, whether instability in weekly mood episode symptoms and other clinical and demographic factors were related to emotional bias as measures in a simple laboratory task.

Methods: Participants (N=271; BDI=206 or BDII=121) completed an 'emotional categorization and memory' task. Weekly self-reported symptoms of depression and mania were collected prospectively. In linear regression analyses, associations between cognitive bias and mood variability were explored together with the influence of demographic and clinical factors, including current medication.

Results: Greater accuracy in the classification of negative words relative to positive words was associated with greater instability in depressive symptoms. Furthermore, greater negative bias in free recall was associated with higher instability in manic symptoms. Participants diagnosed with BDII, compared with BDI, showed overall better word recognition and recall. Current antipsychotic use was associated with reduced instability in manic symptoms but this did not impact on emotional processing performance.

Conclusions: Emotional processing biases in bipolar disorder are related to instability in mood. These findings prompt further investigation into the underpinnings as well as clinical significance of mood instability.

Keywords: Bipolar disorder; mood symptoms; mood instability; emotional processing; emotional bias

INTRODUCTION

Abnormal affective biases have been reported in Bipolar Disorder (BD), including amongst euthymic and clinically stable patient groups. In the majority of studies, the observed emotional bias appears to be negative in nature (Gopin *et al.*, 2011, Lemaire *et al.*, 2014). However, observed patterns of emotional bias are inconsistent, and differences with healthy controls are not always observed (Rock *et al.*, 2010, Venn *et al.*, 2004). Understanding the emotional biases present in BD is important, as they are posited to underpin some of the symptoms of mood disorders as well providing a potential target for therapeutic intervention (Harmer *et al.*, 2009).

Mood instability is regarded as clinically important - if difficult to define – and characterized in part by frequent shifts in affective category, but also incorporating features such as abnormal intensity in affect and exaggerated responses to psychosocial cues (Koenigsberg, 2010). Mood instability is a widely-recognised feature in many psychiatric disorders, including BD (Henry *et al.*, 2008). Greater mood instability in BD, as indexed by the proportion of weeks featuring a shift between euthymia, clinical, and subclinical mood states, has been associated with functional impairment (Strejilevich *et al.*, 2013) pointing to the clinical relevance of inter-episode sub-syndromal mood patterns. Accordingly, successful management of BD is thought to necessitate the maintenance of mood stability. Furthermore, a recent study using daily mood monitoring with 27 euthymic BD patients and healthy controls demonstrated that greater mood instability (measured as mean square successive differences [MSSD] of mood ratings) was correlated with greater functional impairment and was predictive of depressive symptoms (Gershon and Eidelman, 2015). However, nothing is known of how aspects of cognition, including emotional processing, might be associated with fluctuations in mood symptoms.

Inconsistent reports of emotional bias in BD is likely due to a number of factors including varying inclusion criteria and measures of emotional processing, but also small sample sizes and poor classification of current mood. In addition, several studies have reported state-dependent attentional biases in BD (Garcia-Blanco *et al.*, 2013, Murphy *et al.*, 1999). The effects of medication are a further complicating factor, and such effects may be substantial: for example, Holmes et al found that medicated subjects with BD (currently taking lithium or sodium valproate) were both less accurate and slower to respond to happy words as compared to unmedicated subjects with BD in an affective shift task (Holmes *et al.*, 2008). However, many studies have been underpowered to explore the potential effects of medication in patient groups, which are argued to not account for core observations (Garcia-Blanco *et al.*, 2013, Lemaire *et al.*, 2014, Lex *et al.*, 2008). Inconsistencies in previous literature may also be driven by possible differences in emotional processing between BDI and BDII, which few studies have been powered to explore (Mercer and Becerra, 2013).

Here, we explored associations between emotional bias, as measured in an emotional categorisation and memory task, and prospectively-gathered weekly manic and depressive symptoms, in a large, naturalistic cohort of BD patients. Given the evidence linking mood instability with greater impairment in BD, we hypothesized that higher levels of symptom lability would be associated with a well-validated risk factor for affective disorders: greater bias towards negative stimuli. The size of our cohort allowed us to explore the effects on cognition of core demographic and clinical variables (including current mood symptoms, current medication status, and effects of diagnostic subtype), and to determine whether instability in symptoms of mood episodes added anything over and above these more established predictors.

METHODS

Participants

Participants were recruited into the OXTEXT-1 cohort study; recruitment began in 2010 and is ongoing. Here we report data of all participants who completed OXTEXT-1 assessments between 4th May 2010 and 18th June 2014. OXTEXT-1 was approved by Oxfordshire Research Ethics Committee A and written informed consent was obtained from all participants (REC ref 10/H0604/13).

Recruitment into OXTEXT-1 is via three main routes: by referral from an Adult Mental Health Team within Oxford Health NHS Foundation Trust; from posters and fliers that are displayed in the local community; and by clinicians at the Bipolar Disorder Research Clinic at the NIHR-Clinical Research Facility (NIHR-CRF) at the Warneford Hospital (Oxford, UK). Participants were eligible to take part in the study if: they had a primary diagnosis of DSM-IV-R bipolar disorder (BDI, BDII and BD 'not otherwise specified' or NOS); were age 16 years or older; and both willing and able to give informed consent to participate.

Procedure

Research Assessment

All participants completed a single baseline assessment. During this assessment, participants completed an audio-recorded diagnostic interview, adapted from the Mini International Neuropsychiatric Interview (the MINI; Sheehan *et al.*, 1998), and conducted by a trained Research Assistant. All clinical interviews were reviewed by a Research Psychiatrist for diagnostic confirmation. A baseline research questionnaire was used to collect demographic and clinical information including current medications. Participants then completed the Emotional Categorization and Memory Test as part of a battery of neuropsychological tasks. Data relating to

other tasks are not presented here. All participants were then registered on the TrueColours self-monitoring system (see *Mood Assessment,* below) and provided training on how to use the system.

Emotional Categorisation and Memory Test

The 'emotional categorisation and memory' test utilizes positively- and negatively-valenced word stimuli to explore emotional biases in processing. It is comprised of 3 separate tasks and has been previously described (see Harmer *et al.,* 2008). A brief description of the tasks is included below.

Emotional Categorisation task

Participants were presented with 60 positively- or negatively-valenced personality characteristics chosen to be agreeable or disagreeable (e.g. cheerful, generous vs. domineering, hostile; Anderson, 1968). Each word was presented in the center of a laptop screen for a duration of 500ms. Participants were asked to indicate whether they would like or dislike being described as possessing each personality characteristic by pressing one of two keys on the keyboard, as quickly and as accurately as possible.

Emotional Memory task

Following an approximately 15 minute delay, participants were asked to freely recall (and write down), within a two minute time window, as many of the personality trait words from the above Emotional Categorisation task as possible.

Emotional Recognition task

Finally, 120 personality characteristic words were presented in the center of the laptop screen, one at a time and for duration of 500ms. These words consisted of 60 familiar words presented in the first Emotional Categorisation task (30 agreeable; 30 disagreeable) and 60 novel personality

characteristic words (30 agreeable; 30 disagreeable and again taken from Anderson, 1968). Participants were asked to categorise each of the personality traits as either 'familiar' from the first task, or 'novel', and respond by pressing one of two keys on the keyboard as quickly and accurately as possible. Target sensitivities (formula: $\delta' = 0.5 + ((y-x).(1+y-x))/(4y(1-x))$, where y is the probability of correct responses and x is the probability of false alarms) as well as response biases (formula: $\beta = (y(1-y)-x(1-x))/(y(1-y)+x(1-x))$ were calculated. Higher sensitivity has been shown to correlate with higher accuracy in the task, whilst response bias allows filtering of data to remove cases where participants are notably over-favouring 'familiar' or 'novel' responses throughout the task (Mocking *et al.*, 2013).

Mood assessment

All participants were registered to submit mood ratings on a weekly basis by answering text or email prompts from the True Colours self-monitoring system (Miklowitz *et al.*, 2012). Depression ratings were captured with the Quick Inventory of Depressive Symptomology (QIDS; Rush *et al.*, 2003) and the mood elevation ratings with the Altman Self-Rating Mania scale (ASRM; Altman *et al.*, 1997).

Indices of manic and depressive symptoms were extracted from the True Colours system both for the week in which participants undertook the neuropsychological assessment (week 0; denoted W0), and for the proceeding 6 weeks (i.e. W0 to W6). Thus all self-reported measures of depression and mania were collected in the 6- to 7-week period following neuropsychological assessment.

For the purpose of data analysis the ASRM data obtained from True Colours responses were transformed into binary data (<=5 and >5) as data was not normally distributed. ASRM scores

greater than 5 are considered to indicate a manic state, whilst those less than 5 are considered to indicate a non-manic state (Altman *et al.*, 1997).

Mood instability. We used the square root of the Mean Square Successive Difference (MSSD) of weekly QIDS and ASRM scores as a measure of depressive and manic symptom instability. MSSD measures provide an index of data dispersion whilst accounting for variability and the temporal (serial) aspects of data, and has previously been used as a measure for affective instability in BD (Gershon and Eidelman, 2015) and borderline personality disorder (BPD) (Jahng *et al.*, 2008). Square-Rooting of MSSD scores (denoted here as RMSSD) normalises the inherent positive skew of MSSD data for parametric analyses.

Statistical Analysis

All statistical analyses were conducted in SPSS (IBM SPSS Statistics version 22). Chi-squared tests were used to test for differences between diagnostic groups (BDI vs. BDII) in terms of gender, education level (categorized as less than GCSE; O-level/GCSE; A-level or equivalent; Degree/NVQ level 5; and postgraduate degree), current medication (with lithium, antidepressant, antipsychotic, mood stabilizer, or drug free coded as separate binary variables), ethnicity, and baseline evidence for mania (ASRM>5). Diagnostic group differences for continuous variables (e.g. age, baseline depression, and RMSSD values) were tested using independent samples t-tests.

Base model. A base backwards linear regression model was used to test the effects of diagnosis, clinical variables, and mood variables on emotional processing. This base model contained the following independent variables: gender; diagnosis; age; education level; baseline mood (QIDS score and categorical ASRM =<5/>5 at week 0); current medications or drug free status (coded as

dummy variables); and QIDS RMSSD *or* ASRM RMSSD (entered separately). Dependent variables were selected as described below.

Separate linear regression analyses were conducted for each of the following dependent variables. To examine which demographic and clinical factors impacted overall task performance, we entered into the base model (individually) dependent variables of: (i) categorization accuracy; (ii) categorization reaction time; (iii) accurate free recall; (iv) recognition accuracy; and (v) sensitivity in the recognition task. In all cases dependent variables collapsed data across positively- and negatively-valenced trials. We further tested how demographic and clinical variables were associated with emotional bias, by selecting as dependent variables (again individually) (vi) bias in categorization accuracy (positive – negative, such that a positive value reflects an overall positive emotional bias); (vii) bias in accurate recall, (viii) bias in sensitivity (recognition task), and (ix) bias in categorization reaction time (RT).

We also examined whether depressive and manic/hypomanic symptom instability was associated with demographic and clinical variables (e.g. age, diagnostic subtype, current medication). To do this, we re-ran the main linear regression model but with QIDS RMSSD and ASRM RMSSD selected as dependent variables rather than independent variables.

RESULTS

The data of 346 participants were extracted. The total number of participants diagnosed with BD-NOS or those with unconfirmed diagnoses was low (N=24, 6.9%). Early analyses

suggested that data collected from the BD-NOS group was heterogeneous, such that making conclusions based on such a small sample would be challenging. Given that we wished to test for possible effects of the more prevalent BDI and BDII diagnostic subtypes on emotional processing, these participants were therefore excluded from further analysis. Due to procedural changes in the study protocol medication data was not collected within 30 days of testing for a subset of 51 participants (15.0%) which were excluded from further analysis (remaining N=271). For the results reported, each regression analysis included all available data for the variables included in the respective models. Models including RMSSD variables included only those participants who responded at least 4 times to weekly questionnaires during the 7-week period from baseline (W0) to week +6 (W6), leading to the exclusion of 26 participants' data (9.5%) and thus a final sample for the RMSSD analyses of N=245. The groups excluded and included on the basis of response rate are well matched for age, gender and diagnosis (see Supplementary Table 1).

Participant demographics and clinical variables

Demographics and clinical characteristics of the sample is shown in Table 1. As the sample was predominantly Caucasian (94%) ethnicity is presented and analysed as a binary variable (Caucasian vs. non-Caucasian). Means ± standard errors (SE) are provided in the text unless otherwise indicated.

A full comparison of the diagnostic groups (BDI vs. BDII) on the clinical and demographic variables presented in Table 1 is provided in the Supplementary material. Diagnostic groups differed in terms of prevalence of lithium treatment [$\chi^2(1) = 5.386$, $p = 0.020$], with 38% of BDI patients vs. only 24% of BDII patients on lithium. They also differed on the prevalence of

antidepressant treatment [$\chi^2(1) = 4.357$, $p = 0.037$], with 32% of BDI patients vs. 45% of BDII patients on antidepressants. However, the groups did not differ in terms of prevalence of anticonvulsant treatment [$\chi^2(1) = 0.024$, $p = 0.877$], antipsychotic treatment [$\chi^2(1) = 0.699$, $p = 0.403$], or drug free status [$\chi^2(1) = 0.728$, $p = 0.393$].

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Diagnostic groups showed similar values of RMSSD for depressive symptoms at weeks 0-6 [$t(243) = -0.529$, $p = 0.597$] and RMSSD for manic/hypomanic symptoms at weeks 0-6 [$t(243) = -1.122$, $p = 0.263$] (see Table 2).

Demographic and clinical predictors of depressive/manic symptom instability

Current antipsychotic use was associated with decreased instability in manic symptoms (2.75±0.20 compared to 3.30±0.25 for those not taking antipsychotics [B=-0.780(0.343), p=0.024]). As expected, baseline symptomology was significantly and positively related to RMSSD scores. Evidence of mania at baseline (i.e. W0 ASRM scores >5) was associated with significantly higher ASRM RMSSD values (4.79±0.45 vs. 2.57±0.18 [B=2.280(0.402), p<0.001]). Higher levels of baseline depressive symptoms (W0 QIDS scores) were also related to higher QIDS RMSSD values [B=0.088(0.031), p=0.004]. In addition, increased age was linked with lower instability in manic symptoms [B=-0.035(0.013), p=0.008]. Finally, female participants showed higher levels of instability in depressive symptoms compared to male participants (4.06±0.21 vs. 3.39±0.28 [B=0.758(0.364), p=0.039]).

Predictors of overall task performance

Effects of demographic variables (including age, gender, and education) on overall performance on the emotional categorisation and memory tasks are presented in the

Supplementary Material. In brief, participants with higher education levels tended to perform both more quickly and accurately in most tasks, whilst increasing age was associated with poorer performance and slower responses. Females tended to be quicker and more accurate in the majority of tasks compared to males.

Effects of diagnosis. Participants diagnosed with BDII were able to accurately recall more words than BDI participants, but this effect did not reach significance (3.49±0.19 vs. 3.07±0.14, respectively) [B=0.368(0.208), p=0.077]. Participants with BDII were significantly quicker in the recognition task than participants with BDI (1554.53±39.16 vs. 1756.57±48.20 [ms], respectively) [B=-163.771(68.313), p=0.018].

Effects of medication. Participants who were currently drug free demonstrated overall better sensitivity in the recognition task (0.891±0.048 vs. 0.840±0.75) [B=0.030(0.014), p=0.037] whilst those on anticonvulsants demonstrated poorer sensitivity than those not on anticonvulsants (0.830±0.086 vs. 0.856±0.063) [B=-0.020(0.009), p=0.021] and those currently on lithium demonstrating longer reaction times in the recognition task than those not currently taking lithium (1805.82±68.30[ms] vs. 1596.79±32.24) [B=157.155(70.217), p=0.026].

No effects of baseline mood or mood instability were observed on behavioural outcomes related to overall task performance.

Predictors of emotional bias

Effects of diagnosis. No effects of diagnosis on emotional bias (as indexed by positive vs. negative categorisation accuracy, free recall, recognition accuracy, or categorization reaction time) were observed.

Effects of medication. Those participants who were drug free were quicker to categorise negative words relative to positive words as compared with participants on any psychotropic medication (mean difference in categorisation reaction time -62.09±8.91 for participants on any medication, -18.94±30.05 for medication-free) [B=85.101(32.951), p=0.011] (see also Supplemental Table 2).

Effects of baseline mood symptoms. Participants scoring >5 on the ARSM at baseline demonstrated greater accuracy for categorization of positive words relative to negative words (0.62±0.64 vs. -0.55±0.23) ([B=1.326(0.518), p=0.011]. Participants with a higher baseline QIDS score were faster to categorize negative words relative to positive words in the categorization task [B=3.445(1.525), p=0.025].

Effects of mood instability on emotional bias

Greater categorisation accuracy for negative words relative to positive words was related to higher instability in depressive symptoms [B=-0.204(0.092), p=0.027] (Figure 1). In the recall task, greater relative recall of negative words was related to higher instability in manic symptoms [B= -0.124(0.055), p=0.026] (Figure 2). No other associations between symptom instability and emotional bias were observed.

Exploration of R^2 values determined that the explained variance in categorization accuracy of negative vs. positive words, including instability in depressive symptoms (QIDS RMSSD) as a regressor, was 16.9%. Removing QIDS RMSSD from the model caused a drop in variance explained by 2.3% (to 14.6%). The total variance explained in recall of positive relative to negative words was 3.2%, which reduced by 1.7% when instability in manic symptoms was removed from the model.

DISCUSSION

We observed that greater instability for depressive symptoms and manic symptoms correlated with negative biases in categorisation and memory, respectively. In addition, ~~a number of associations between current medication use, current mood symptoms, and emotional bias or mood instability were observed. This included~~ we observed an association between greater positive bias (faster responses in categorising positive compared to negative words) and current medication use as compared with non-use, as well as mood-congruent effects on emotional processing, such that higher levels of current depressive symptomology were related to greater negative bias (faster categorization of positive relative to negative words) whilst self-reported levels of substantive manic symptoms were related to greater positive bias (more accurate categorization of positive relative to negative words). Additionally, current antipsychotic use

was associated with reduced instability in manic symptoms. Notably, we find no evidence that a diagnosis of BDI or BDII mediates emotional bias, although some evidence of more general cognitive impairment in BDI was found.

Our results are the first to draw links between emotional biases and instability in both depressive and manic symptoms in BD. ~~Mood variability has received relatively little attention in previous clinical research, but is known to be important in both euthymic and symptomatic patients with bipolar disorder (Malhi *et al.*, 2014, Strejilevich *et al.*, 2013). Emotional biases in mood disorders have been the focus of more extensive research, for example when investigating effects of medication (Harmer *et al.*, 2009) and markers conferring vulnerability to future mood episodes (Gotlib and Krasnoperova, 1998).~~ The degree of variance in behaviour data explained by self-reported symptom instability was modest. Nevertheless, our result thus suggests that mood instability in BD may be related to underlying, and potentially clinically relevant, patterns of emotional information processing. That frequent shifts in mood state were related to maladaptive patterns of information processing might be understood in terms of *cognitive reactivity*, whereby changes in affect – including sub-syndromal changes - may reactivate cognitive patterns that were present during past mood episodes (Lau *et al.*, 2004). Here, instability in both manic and depressive symptoms were linked to increased negative emotional bias, evidence that fluctuations in the symptoms of *either* affective polarity are clinically meaningful. It is possible that the shifting of mood in and of itself is important in underpinning the pathology of BD, as well as the experience of mood episodes. More frequent or exaggerated mood shifts, whether towards the manic or depressive pole, may be associated with de-stabilized cognitive schemas. Effective coping strategies may also need to be more adaptive and dynamic, and more challenging therefore to develop or maintain. Variability in mood, uncertainty for the individual in predicting mood changes, and destabilization of

cognitive schemas and coping strategies may lead to weighting of information processing towards more negatively-valenced cognitive stances, in a disorder where depressive symptoms are known to dominate the longitudinal course, and where depressive symptoms and episodes may be more sailent.

In contrast, current mood state appeared to have differential effects on emotional processing, with current depressive and manic symptoms associated with greater negative and positive bias, respectively (as observed also by others; Garcia-Blanco *et al.*, 2013, Murphy *et al.*, 1999). That mood instability is more parsimoniously linked to cognitive bias may highlight the importance of affective lability in understanding the pathology of BD as well as promote it as a potential target in experimental models of treatment efficacy.

Our findings also add to a body of work suggesting that medications used in the treatment of mood disorders may exert their therapeutic effects via the modification of emotional information processing patterns. ~~We observed that c~~Current use of medication as compared with non-use in our bipolar cohort was associated with more positive bias, as measured by faster categorisation of positive relative to negative word stimuli. Notably, in one of the few other studies to explore emotional biases in a community sample of depressed patients, current use of any medication (as compared with non-use) was associated with enhanced processing of positive stimuli in patients with major depressive disorder (Wells *et al.*, 2014). The current findings are therefore consistent with the hypothesis that medication used in bipolar illness may also enhance the processing of positive cues, though this needs to be examined in a controlled experimental design to rule out the influence of possible confounders.

Our data also point to the potential effects of antipsychotic medication in reducing lability in manic symptoms amongst our patient participants. This observation is consistent with previous clinical research linking antipsychotic use with the amelioration of manic symptoms in bipolar disorder (Vieta and Goikolea, 2005). In addition, a recent review has suggested that olanzapine and aripiprazole significantly reduce mood instability in borderline personality disorder (Bellino *et al.*, 2012). Although establishing the effects of medications necessarily involves carefully controlled experimental work, our data collected from a naturalistically recruited cohort of BD patients highlight the potential of antipsychotic treatments to stabilize manic symptoms in BD over time, rather than solely reduce symptoms at a given time point: greatest clinical benefit is likely to involve both.

We observed that BDI as compared to BDII was associated with relatively impaired free recall, and slower responses in word recognition, but diagnostic groups did not differ in terms of emotional processing outcomes. This is broadly consistent with previous literature, which has focused on predominantly non-affective cognitive function, and points to greater levels of cognitive impairment in BDI compared to BDII (Bourne *et al.*, 2015, Hsiao *et al.*, 2009, Simonsen *et al.*, 2008). Of the few other studies comparing BDI and BDII groups on affective cognitive function, results seem to be inconsistent (Mercer and Becerra, 2013). For example, one previous study found that euthymic BDI participants were worse at labelling some emotional facial expressions compared to BDII participants (Derntl *et al.*, 2009) whilst another found no differences between groups (Lembke and Ketter, 2002). Our results lend support to the idea that emotional processing in BDI and BDII do not differ substantially, based on an analysis of a large cohort in which we could concurrently explore the effects of both current mood symptoms and medications on cognitive performance.

Limitations

This is the first study to explore the association between emotional bias and symptom instability in BD. However, the conclusions that can be drawn on the basis of these data are subject to a number of important caveats. Firstly, we had no data from a matched healthy control group, without which it is unclear what patterns of emotional bias and mood instability might be within the normal range. As this is the first study - to the best of our knowledge - which reports emotional processing in BD as measured in the emotional categorization and memory task, our approach was exploratory. We did not correct for multiple comparisons, and thus our findings require replication. Our data suggest that emotional biases may be predictive of symptom variability, but establishing this causal relationship is beyond the scope of this correlational study; we also lacked mood data in the weeks prior to task completion, which limited the extent to which we could explore the temporal relationship between mood and emotional bias. The putative effects of current medication on emotional bias may be driven by unknown clinical variables which differentiate those patients who receive pharmacotherapy from those who do not, although there is no evidence to suggest that patients who are concordant with medication are more likely that those who are not to have a pre-existing positive cognitive bias.

Whilst medication information was available for this sample, and was included in our analyses - unlike many other studies (Gershon and Eidelman, 2015, Gopin *et al.*, 2011, Lex *et al.*, 2008) - we did not collect information about dosage. We did not screen for comorbid axis I or axis II disorders, raising the possibility that some of our findings are driven by symptom patterns associated with personality disorders. In particular, traits of BPD, characterised itself in part by lability of mood, and frequently co-morbid with BD (Magill, 2004) might have been expected to have influenced our findings.

Reliance on patient- reported mood episode may have introduced bias into mood data, although previous research shows promising agreement between self-report and clinician-reported longitudinal symptoms in BD (Born *et al.*, 2014). The sensitivity of our symptom-tracking approach to detecting mood fluctuations is still unclear, but was pragmatic in enabling un-intrusive data collection on a larger scale, and possibly with higher compliance, than might otherwise be feasible. Finally, the best methods of characterizing and quantifying mood instability, including frequency and length of overall time-frame of mood sampling, remain uncertain. Although we used a measure of mood instability which been employed in previous research (Jahng *et al.*, 2008) other measures of signal variability exist (see Garrett *et al.*, 2013) and may prove to be more sensitive, but typically require more data-points than were available in the present study. Our mood episode data was gathered on a weekly basis, although fluctuations on finer time-scales are likely to be clinically relevant. New mobile technologies are making frequent sampling of mood increasingly practicable (Faurholt-Jepsen *et al.*, 2013).

In conclusion, our data suggest that maladaptive emotional biases may be associated with greater mood variability in BD. The observed links between medication use, emotional bias, and mood patterns point to the clinical relevance of emotional biases in BD, as well as the potential of both emotional bias and quantified mood instability to act as potential therapeutic targets or markers of treatment response.

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Conflicts of Interest

GMG reports grants and personal fees from Servier, personal fees from Teva, personal fees from Otsuka, personal fees from Takeda, grants and personal fees from Lundbeck, personal fees from Ei Lilly, personal fees from Merck, personal fees from GlaxoSmithKline, personal fees from Astra Zeneca, and grants from P1vital during the conduct of the study. CJH has received consultancy fees from Lundbeck, Servier and P1vital. She has shares in P1vital and also is a company director and shareholder of Oxford Psychologists Ltd. CJH has received grant funding from J&J, UCB, Lundbeck, Sunovion, Astra Zeneca, Servier and GSK. All other authors declare no conflicts of interest.

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TABLES

Table 1. Demographic and clinical characteristics of participants. Values are numbers of cases (percentages in brackets) unless otherwise specified.

	Total N=271		
	Diagnosis		Overall
	BDI (N=164)	BDII (N=107)	
Mean age (SEM, range), years	41.1 (1.0, 17-76)	39.4 (1.4, 17-72)	40.4 (0.8, 17-76)
Female gender	110 (67%)	75 (70%)	185 (68%)
Ethnicity			
Caucasian	156 (93%)	100 (93%)	256 (94%)
Education level*			
Less than GCSE	7 (4%)	8 (7%)	15 (6%)
O-level/GCSE	19 (12%)	12 (11%)	31 (12%)
A-level or equivalent	42 (26%)	30 (29%)	72 (27%)
Degree/NVQ level 5	52 (32%)	26 (25%)	78 (29%)
Postgraduate degree	41 (25%)	29 (28%)	70 (26%)
Mean QIDS score, W0 (SEM, range)	8.9 (0.5, 0.0-24.0)	11.7 (0.7, 2.0-24.0)	9.9 (0.4, 0.0-24.0)
Median ASRM score, W0 (range)	2 (0-17)	2 (0-20)	2 (0-20)
Ever admitted for depression	79 (48%)	42 (39%)	121 (45%)
Ever admitted for mania	88 (54%)	0 (0%)	88 (33%)
Mean impairment age			
Depression (SEM, range), years	21.9 (0.74, 4.0-54.0)	20.4 (0.9, 7.0-57.0)	20.7 (0.6, 4.0-57.0)
Mania (SEM, range), years	26.0 (0.91, 3.0-72.0)	25.4 (1.1, 11.0-61.0)	25.8 (0.69, 3.0-72.0)
History of suicide attempt	82 (50%)	36 (34%)	118 (44%)
Current medications			
Lithium	62 (38%)	26 (24%)	88 (32%)
Anticonvulsants	69 (42%)	44 (41%)	113 (42%)
Antipsychotics	79 (48%)	46 (43%)	125 (46%)
Antidepressants	53 (32%)	48 (45%)	101 (37%)
None (drug free)	16 (10%)	14 (13%)	30 (11%)

* Educational information missing for 3 BDI participants and 2 BDII participants. Percentages are reported with regards to the data available.

Table 2. RMSSD values, as a measure of mood instability

Total N= 245				
	Diagnosis			
	BD1		**BD2**	
	Mean	**SEM**	**Mean**	**SEM**
QIDS RMSSD (weeks 0-6)	3.77	0.21	3.95	0.27
ASRM RMSSD (weeks 0-6)	2.87	0.19	3.25	0.30

RMSSD = Root Mean Square Successive Difference

QIDS=Quick Inventory of Depressive Symptomology

ASRM=Altman Self-Rated Mania scale

FIGURE LEGENDS

Figure 1. Scatterplot, with a line of best fit, showing the mean difference in categorization accuracy (positive – negative; higher values are indicative of greater positive bias) against QIDS RMSSD. The relationship between bias in categorization accuracy and QIDS RMSSD remains significant after the removal of a potential outlier (filtering out difference in categorization accuracy>20, [B=-0.163(0.081), p=0.045])

Figure 2. Scatterplot, with a line of best fit, showing the mean difference in free recall (positive – negative; more positive values are indicative of greater positive bias) against ASRM RMSSD.